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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

NOTIFICATION DATE	DELIVERY MODE
05/14/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/521,410	ULLRICH ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-9,11,13 and 20-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 12, 14-19, and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed February 19, 2008 in response to the Office Action of October 19, 2007 is acknowledged and has been entered. Claims 10, 12, 16-18 have been amended and new claim 35 has been added.

2. Claims 10, 12, 14-19 and 35 are under consideration drawn to the AXL protein and an antibody directed against the Axl protein.

3. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10, 12, and 14-19 remain rejected and new claim 35 is rejected essentially for the reasons set under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement essentially for the reasons set forth in the Office Action of October 19, 2007, sections 7 and 8, pages 4-16.

Applicants argue that the specification provides in vivo and reliable in vitro data to support the pending claims. The specification provides in vivo data from tumor cells subcutaneously implanted into nude mice (a reliable model) with subsequent intravital microscopy and histomorphological analyses. See Figure 9 and p. 13, line 20- p.14, line 16; p. 33, line 15 - p. 34, line 25, p. 35, line 24 - p. 36, line 13; Figure 11 and p. 15, lines 9-16 of the present specification. The results here showed impaired tumorigenicity, reduced tumor growth, lack of tumor invasion, and increased sensitivity towards serum withdrawal (apoptosis) after

implantation of cells with a truncated, dominant-negative mutant form of human UFO/AXL lacking the intracellular RTK-bearing domain. See p. 32, line 22- p. 33, line 5; p. 33, line 15- p. 34, line 13; p. 38, lines 27-32 of the present specification. Applicants argue that the in vivo data provide support that the claimed method will function as a therapeutic cancer drug.

Applicants' arguments have been considered, but have not been found persuasive. Although tumor growth and invasion are suppressed by a dominant negative UFO/AXL protein engineered to be expressed in a tumor cell *in vitro*, no evidence has been presented that such a mutant protein can be delivered to or expressed in a cancer cell *in vivo* without the prior engineering of the cells *in vitro*. Additionally no empirical evidence has been presented that an antibody or any other agents directed against AXL can reduce the invasivity of cancer cells *in vivo*. Thus, although one could predictably reduce the invasivity of cancer cells *in vitro* by inhibiting the Axl protein, given the unpredictability in the art of the development of cancer therapeutics and the refractory nature of cancer to drugs previously set forth, one of skill in the art one of skill in the art would not predictably be able to reduce the invasivity of cancer cells that are susceptible to Axl suppression *in vivo*.

Applicants argue that *in vitro* tests were conducted on MatrigelTM-matrix (3D outgrowth), as described in the references 101, 112, and 12 3 cited in the present application, in order to show morphologies and to assay invasion activity and migration ability. These tests are described at p. 20, line 23 - p. 22, line 3; p. 25, line 19- p. 26, line 5 of the present application. See also p. 9, line 1-15 and Figure 1; p. 11, line 25- p. 13, line 4 and Figures 5-7. Reference 10, in particular, describes the benefits and accuracy of using a MatrigelTM for measuring invasiveness of tumor cells, showing that this model predicts in vivo behavior. These in vitro

tests on MatrigelTM showed that the dominant negative mutant of the AXL gene (dnAXL) strongly suppressed invasiveness, migration and survival of cells and that a polyclonal antibody directed against the extracellular portion of the AXL protein strongly inhibited migration and invasion of tumor cells. See p. 26, lines 14-31. Applicants argue that the above testing, both in vivo and in an in vitro assay known in the art to reliably predict in vivo activity, show that the skilled person would have been able to practice the invention as claimed

Applicants' arguments have been considered, but have not been found persuasive because *in vitro* assays are not reliably predictive of *in vivo* activity as previously set forth. Thus, although one could predictably reduce the invasivity of cancer cells *in vitro* by inhibiting the Axl protein, given the unpredictability in the art of the development of cancer therapeutics and the refractory nature of cancer to drugs previously set forth, one of skill in the art one of skill in the art would not predictably be able to reduce the invasivity of cancer cells that are susceptible to Axl suppression *in vivo*.

Applicants argue that the specification also discloses data showing that inhibited AXL protein function resulted in reduced invasivity. For example, western blot analysis demonstrated that an antibody directed against the human AXL protein inhibits AXL-mediated signaling (see p. 13, lines 6-18 and Figure 8; p. 28, line 18- p. 29, line 7; p. 32, line 21 - p. 33, line 13). In addition, a truncated, dominant-negative mutant form of human UFO/AXL lacking the intracellular RTK-bearing domain abolished Gas6/UFO/AXL-mediated signaling. See p. 13, lines 6-18; p. 32, line 21 - p. 33, line 13.

Applicants' arguments have been considered, but have not been found persuasive. The specification does not show that the Axl antibody inhibited Axl signaling, the Axl antibody was

simply used for detection of the Axl protein in assays of the dnAXL's effect on signaling. Although a truncated, dominant-negative mutant form of human UFO/AXL lacking the intracellular RTK-bearing domain abolished Gas6/UFO/AXL-mediated signaling, no evidence has been presented that such a mutant protein can be delivered to or expressed in a cancer cell *in vivo* without the prior engineering of the cells *in vitro*. Additionally no empirical evidence has been presented that an antibody or any other agents directed against AXL can reduce the invasivity of cancer cells *in vivo*. Thus, although one could predictably reduce the invasivity of cancer cells *in vitro* by inhibiting the Axl protein, given the unpredictability in the art of the development of cancer therapeutics and the refractory nature of cancer to drugs previously set forth, one of skill in the art one of skill in the art would not predictably be able to reduce the invasivity of cancer cells that are susceptible to Axl suppression *in vivo*.

Applicant's arguments have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 10, 12, 14-19, and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "cancer cells that are susceptible to Axl suppression" renders claims 10, 12, 14-19, and 35 as the term is not defined by the claim and the specification does not teach what "cancer cells that are susceptible to Axl suppression" are. Thus it is unclear what cancer cells that are susceptible to Axl suppression are.

Section 2171 of the M.P.E.P. states

There are two separate requirements set forth in this paragraph:
(A) the claims must set forth the subject matter that applicants regard as their invention; and
(B) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.

The first requirement is a subjective one because it is dependent on what the applicants for a patent regard as their invention. The second requirement is an objective one because it is not dependent on the views of applicant or any particular individual, but is evaluated in the context of whether the claim is definite — i.e., whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art.

In the instant case of "cancer cells that are susceptible to Axl suppression", one of skill in the art could find representative examples in the art which have been defined in such terms, however, it is unclear at what point one of skill in the art would be infringing on the claims without limitations as to when cells are cancer cells that are susceptible to Axl suppression and when they are not.

6. Claims 10, 12, 14-19, and 35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation of "cancer cells that are susceptible to Axl suppression" claimed in claims 10, 12, 14-19, and 35 has no clear support in the specification and the claims as originally filed. A review of the specification by the Examiner did not reveal support for the newly claimed

limitation. Thus, the subject matter claimed in claims 10, 12, 14-19, and 35 broadens the scope of the invention as originally disclosed in the specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 10, 12, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No.: 5,468,634 (Liu, November 21, 1995).

The claims are drawn to:

10. A method of reducing the invasivity of cancer cells that are susceptible to AXL suppression comprising inhibiting AXL protein activity, interaction between AXL protein and its ligands, or a combination thereof.

12. The method of claim 10 comprising inhibiting the receptor tyrosine kinase activity of the AXL protein.

14. The method of claim 10 comprising inhibiting the interaction between the AXL protein and its ligands

It is noted that given the broadest reasonable interpretation of amended claims 10, 12, and 14, the claims read on both in *vitro* and *in vivo* reduction of invasivity of cancer cells that are susceptible to AXL suppression.

Given the indefinite nature of the claims, it is assumed for examination purposes that "cancer cells that are susceptible to AXL suppression" are cancer cells expressing Axl.

US Patent No.: 5,468,634 teaches contacting tumor cells with Axl antibodies that inhibit Axl receptor function by either blocking receptor function or through down regulation of the receptor for *in vitro* diagnostic and therapeutic purposes, see col. 3, lines 14-18, and col. 7, line 60 to col. 8 line 30.

Although the reference does not specifically state the contacting tumor cells with Axl antibodies that inhibit Axl receptor function is a method of reducing the invasivity of cancer cells that are susceptible to AXL suppression, given that the described down regulation of the Axl receptor with the antibodies will inhibit Axl's tyrosine kinase activity and Axl's interaction with its ligands, the claimed method appears to be the same as the prior art method, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from that taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA).

8. All other objections and rejections recited in Office Action of October 19, 2007are withdrawn.

9. No claims allowed.

10. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

11. Applicant's amendment necessitated the new grounds of rejection. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

> A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642

/P. J. R./

/Karen A Canella/

Primary Examiner, Art Unit 1643